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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JIANG, SHAOJIA A	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 08/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/486,839	ACHARI ET AL.	
	Examiner	Art Unit	
	Shaojia A. Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's amendment and response filed on June 3, 2005 wherein claims 23-28 have been cancelled; claims 29-50 are newly submitted. Claims 1-22 are cancelled previously.

Currently, claims 29-50 are pending in this application.

Claims 29-50 are examined on the merits herein.

The following is new rejection(s) necessitated by Applicant's amendment filed on June 3, 2005, wherein all pending claims 23-28 are cancelled and the limitations in the new claims have been changed. Therefore, all rejections of record in the previous Office Action February 8, 2005 are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-32, 37-43, and 48-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment submitted June 3, 2005 with respect to these amended claims have been fully considered but is deemed to insert new matter into the claims.

The omission of an essential element of the invention "a buffer salt in a concentration below about 200 mM,100, 50, or 20mM" in these claims, is deemed to raise new matter issue, i.e., an issue regarding whether the inventor had possession of a broader, more generic invention. See, e.g., >PIN /NIP, Inc. v. Platte Chem. Co., 304 F.3d 1235, 1248, 64 USPQ2d 1344, 1353 (Fed. Cir. 2002). As noted in MPEP 2163, A claim that omits an element which applicant describes as an essential or critical feature of the invention originally disclosed does not comply with the written description requirement. See Gentry Gallery, 134 F.3d at 1480, 45 USPQ2d at 1503; In re Sus, 306 F.2d 494, 504, 134 USPQ 301, 309 (CCPA 1962).

In the instant case, the specification and claims as originally filed clearly disclose the buffer salt in the particular concentration limitation since one of skill in the art would clearly recognize if the buffer salt in the particular concentration is absent, there would not be a stable pH value in the solution herein.

Consequently, there is nothing within the instant specification which would lead the artisan in the field to believe that Applicant was in possession of the invention as it is now claimed. See *Vas-Cath Inc. v. Mahurkar*, 19 USPQ 2d 1111, CAFC 1991, see also *In re Winkhaus*, 188 USPQ 129, CCPA 1975.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Keith (WO 83/00286, of record) in view of Kondrat'eva et al. and JOSHI et al. (5,252,318, of record) and *Handbook of Pharmaceutical Excipients*, 2nd Ed, page 383, of record, further in view of "Remington: The Science and Practice of Pharmacy" (17th ed.), A.R. Gennaro, 1985, page 1308 and 1159 and Applicant admission regarding the prior art in the specification (see page 7-8).

Keith discloses that an intranasal formulation comprising scopolamine hydrochloride in a pharmaceutically acceptable carrier, an aqueous solution containing ethanol, an aerosol spray vehicle, to be administered to a patient (a human), is useful in a method of preventing and/or treating motion sickness such as nausea and/or vomiting. See abstract, Examples I-XII, and claims 1-6. Keith also discloses that the intranasal formulation therein provides quick relief from motion sickness and the onset of effect is within ten minutes. See page 2 lines 3-4, page 3 Example II, and page 4 Example IV.

The prior art does also not expressly disclose the employment of polyvinyl alcohol (PVA), glycerin, a preservative which is benzalkonium chloride, in the formulation in the intranasal formulation and method for the treatment of motion sickness. The prior art does not expressly disclose that the pH value of the instant

intranasal formulation is below about 4 or 3.5, and the concentration of the buffer salt in the instant intranasal formulation is below or equal to100, 50, or 20mM.

Kondrat'eva et al. teaches that the addition of poly(vinyl alcohol) (also known as PVA) (2.5%) to 0.25% aqueous solution preparation of scopolamine-HBr (hydrobromide), significantly increased the stability of the solution of scopolamine-HBr. The eye drops did not show change after sterilization at 120.degree. for 8 min and were stable during 1-year storage. The modified preparation had no irritating effect on the eye. See the English abstract. Note that the eye drop is to be administered to a patient (a human).

Joshi et al. discloses that drug delivery systems such as gelling aqueous compositions therein undergo significant changes in viscosity in response to substantially changes in pH and temperature (see abstract). Joshi et al. also teaches that by adjusting or controlling the pH of these drug delivery systems in an aqueous base through the addition of buffering agents, the viscosities of the compositions or formulations may be various (see col.1 lines 6-15, and col.2 lines 1-5 and 21-28). Joshi et al. also discloses that compositions or formulations therein exhibit steady state flow characteristics at or near room temperature at a pH range of 2.5 to 6.5, i.e., a pH of between 3.0 and 5.0 (see col.3 lines 33-35, and col.7-8 especially lines 57-59). Joshi et al. discloses the employment of lubricants such as polyvinyl alcohol (see col.12 lines 21-22) in combination with one or more additional gelling agents or bioadhesives in the formulations (see col.3 lines 24-48). Joshi et al. further discloses that the most

promising drugs for incorporating into the aqueous drug delivery compositions therein include scopolamine (see col.11 lines 32-33).

Handbook of Pharmaceutical Excipients teaches polyvinyl alcohol is a known viscosity increasing agent (also known as a thickening agent) and a known lubricant (page 383).

"Remington: The Science and Practice of Pharmacy" (17th ed.), A.R. Gennaro, 1985, page 1308 and 1159. teaches that glycerin (also known as glycerol) is an old and well known pharmaceutically acceptable solvent, miscible with water, used in pharmaceutical compositions; benzalkonium chloride is an old and well known antibacterial agent used as a preservative.

More importantly, Applicant admits and acknowledges in the specification (see page 7, line 24 to page 8 line 2) stating that "In the present invention, many other excipients, known from the pharmaceutical literature, may be added to the formulations, such as preservatives, surfactants, co-solvents, adhesives, antioxidants, buffers. viscosity enhancing agents and agents to adjust the pH or the osmolarity" (emphasis added).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ polyvinyl alcohol (PVA), glycerin, a preservative which is benzalkonium chloride, in the formulation in the intranasal formulation and method for the treatment of motion sickness, and to optimize the pH of the intranasal formulation herein to about 3.5 and the concentration of the buffer salt in the instant intranasal formulation to below about 20 mM.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ polyvinyl alcohol, glycerin, a preservative which is benzalkonium chloride, in the formulation in the intranasal formulation and method for the treatment of motion sickness, since an intranasal formulation comprising scopolamine hydrochloride in a pharmaceutically acceptable carrier broadly, an aqueous solution, is known to be useful in a method of preventing and/or treating motion sickness such as nausea and/or vomiting, according to Keith.

Polyvinyl alcohol is known to significantly increase the stability of scopolamine-HBr in aqueous solution, e.g., the scopolamine-HBr solutions did not show change after sterilization at 120.degree. for 8 min and were stable during 1-year storage according to Kondrat'eva et al. Moreover, polyvinyl alcohol is a known viscosity increasing agent (also known as a thickening agent) and a known lubricant, used in the aqueous drug delivery compositions therein include scopolamine according to Joshi et al. and *Handbook of Pharmaceutical Excipients*.

Thus, the motivation and benefit to add polyvinyl alcohol into the intranasal scopolamine formulation of Keith, as claimed herein, increasing the stability of scopolamine-HBr in aqueous solution and increasing viscosity used in the aqueous drug delivery compositions for scopolamine, are seen to be provided by the cited prior art.

Further, glycerin and a preservative such as benzalkonium chloride are excipients, well known from the pharmaceutical literature, to be added to the formulations as Applicant admits and acknowledges in the specification.

Additionally, one having ordinary skill in the art at the time the invention was made would have been motivated to optimize the pH of the instant intranasal formulation to about 3.5 and the concentration of the buffer salt in the instant intranasal formulation to about 20 mM, since gelling aqueous compositions in drug delivery systems are known to significantly change in viscosity in response to changes in pH and temperature according to Joshi et al. Joshi et al. also teaches that by adjusting or controlling the pH of these drug delivery systems in an aqueous base through the addition of buffering agents, the viscosities of the compositions or formulations may be various. Gelling aqueous compositions or formulations therein are known to exhibit steady state flow characteristics at or near room temperature at a pH range of 2.5 to 6.5, i.e., a pH of between 3.0 and 5.0 according to Joshi et al. Scopolamine is known to be one of the most promising drugs for incorporating into the aqueous drug delivery compositions of Joshi et al.

Therefore, one of ordinary skill in the art would found it obvious to optimize the pH by adjusting the concentration of buffering agents in order to make the formulations herein having optimized viscosities exhibiting steady state flow characteristics at or near room temperature since the optimization of parameters based on the known information, i.e., known pH range of 2.5 to 6.5, is considered well in the competence level of an ordinary skilled artisan in pharmaceutical science, involving merely routine skill in the art. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980). Thus, Joshi et al.

clearly provided the motivation and knowledge to optimize the pH and concentration of the buffering agents in the drug delivery system for scopolamine.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Response to Argument

Applicant's arguments filed June 3, 2005 with respect to the rejection made under 35 U.S.C. 103(a) of record in the previous Office Action February 8, 2005 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as further discussed below.

Applicant argues that the combined teachings of the cited reference provide no direct suggestion or motivation to make the claimed invention herein by attacking each reference individually.

One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 SPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145. It must also be recognized that any judgment on obviousness takes into account knowledge which was generally available and within the level of ordinary skill at the time the claimed invention was made. Knowledge of those skilled in art and nature of problem solved provided motivation and made obvious a combination of elements -- Princeton Biochemicals, Inc. v. Beckman Coulter, Inc. 04-1493 -- On June 9, 2005, recently the Federal Circuit upheld a finding of obviousness of Princeton's capillary electrophoresis device, used to separate proteins and other

matter. This court upheld that motivation to combine the elements came from the knowledge of those skilled in the art and the nature of the problem solved by the invention.

In this case, polyvinyl alcohol is known to significantly **increase** the **stability** of scopolamine-HBr in aqueous solution, e.g., the scopolamine-HBr solutions did not show change after sterilization at 120.degree, for 8 min and were stable during 1-year storage according to Kondrat'eva et al. Moreover, polyvinyl alcohol is a known viscosity increasing agent (also known as a thickening agent) and a known lubricant, used generally in the aqueous drug delivery compositions include scopolamine according to Joshi et al. and *Handbook of Pharmaceutical Excipients.*

Thus, the motivation and benefit to add polyvinyl alcohol into the intranasal scopolamine formulation of Keith, as claimed herein, increasing the stability of scopolamine-HBr in aqueous solution and increasing viscosity used in the aqueous drug delivery compositions for scopolamine, are seen to be provided by the cited prior art.

Further, glycerin and a preservative such as benzalkonium chloride are excipients, well known from the pharmaceutical literature, to be added to the formulations as Applicant admits and acknowledges in the specification.

Additionally, one having ordinary skill in the art at the time the invention was made would have been motivated to optimize the pH of the instant intranasal formulation to about 3.5 and the concentration of the buffer salt in the instant intranasal formulation to about 20 mM, since gelling aqueous compositions in drug delivery systems are known to significantly change in viscosity in response to changes in pH and

temperature according to Joshi et al. Joshi et al. also teaches that by adjusting or controlling the pH of these drug delivery systems in an aqueous base through the addition of buffering agents, the viscosities of the compositions or formulations may be various. Gelling aqueous compositions or formulations therein are known to exhibit steady state flow characteristics at or near room temperature at a pH range of 2.5 to 6.5, i.e., a pH of between 3.0 and 5.0 according to Joshi et al. Scopolamine is known to be one of the most promising drugs for incorporating into the aqueous drug delivery compositions of Joshi et al.

Therefore, the combined teachings of the cited references have clearly provided the knowledge of those skilled in art and nature of problem solved. The claimed invention is clearly obvious in view of the prior art.

Again, as pointed in the previous Office Action, Applicant's assertion that Formulation 2 of the specification demonstrates unexpected superior property has been considered. However, the clear explanation of pointing out exactly what facts are established therein and relied upon by applicant is not seen in the specification (see page 20). Applicant has the burden to explain the experimental evidence. See *In re Borkowski and Van Venrooy* 184 USPQ 29 (CCPA 1974).

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejection is adhered to.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
Primary Examiner
Art Unit 1617
August 11, 2005